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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/767,421	01/22/2001	Michael J. Shamblott	JHU1750-1	9551

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/767,421	SHAMBLOTT ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9-13,15,16 and 22-33* is/are pending in the application.

4a) Of the above claim(s) *33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9-13,15,16 and 22-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 19, 2005 has been entered. Claims 1, 9-13, 15, 16, 22-33 are pending, with claim 33 being withdrawn from consideration. Claims 1, 9-13, 15, 16, and 22-32 are examined in this office action.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 lacks antecedent basis in claim 22 for the term "EBD cell culture." Further, claim 23 is confusing as claim 22 states "a constituent cell" and claim 23 states "selecting a single cell." Thus, claim 23 doesn't further limit claim 22 as claim 22 is to culturing "a cell". The difference in scope between claims 22 and 23 is not clear. For examination purposes, claim 22 has been interpreted as if "a constituent cell" is a population of cells in view of the office's policy of compact prosecution and in view of the confusion of claim scope.

Claims 22 states "reduced serum." However, reduced serum is not defined in the specification nor does it have a clear meaning in the art. The only definition of "reduced serum" in the specification is 5% (page 67, line 6). Applicant needs to point to clear definition of the term so that the metes and bounds are known.

Applicant argues that a description of "reduced serum" can be found in the art and the specification. Applicant points to page 57, parag. 0163, page 46, parag. 0134. These

arguments are not persuasive. Applicant provides a summary of Clonetics™ Endothelial Media Systems. These arguments are not persuasive

Still there is no clear description or definition as to the metes and bound of "reduced serum." There are no such paragraphs on pages 46 and 57 of the specification. The Clonetics™ product summary does not define "reduced serum," while it mentions serum concentrations. On page 18, lines 9-16 a range of 1% to 25% is given for use in the invention, although not in the context of "reduced." If some uses 25% is this reduced? 14.5%? 0.5%? The question to be answered is when will someone infringe the claims? Also, reduced in comparison to what standard? A media having 10% serum is reduced compared to a media using 15% serum, but there is no definition in the specification that indicates this is within applicant's definition of reduced. Further, a media having 15% is reduce with respect to a media have 25% serum, but again there is no indication at a 10% or 15% serum containing media is reduced. Applicant needs to rewrite the claim unless a specific definition can be found. Serum-free obviously has no such problem because it clearly means media without any serum. A definition like this is what applicant needs to find in the specification or routinely used in the art.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a

whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 9-13 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Shamblott et al (1998) Proced. Natl. Acad. Sci. 95, pp. 13726-13731.

Claim 1 is drawn to an enriched population of cells comprising cells not having teratogenic properties in SCID mice, and express at least a first and second polypeptide or mRNA marker from at least two different cell types, wherein the cell types are selected from ectodermal cells, mesodermal cells, or endodermal cells, and wherein the first marker is selected from the group consisting of nestin, vimentin, neurofilament light isoform, microtubule-associated protein 2c, tau, nonphosphorylated heavy isoform, neuron-specific enolase, tyrosine hydroxylase, glial fibrillary acidic protein, CNPase, and galactocerebroside, and the second marker is selected from the group consisting of myf-6, myosin light-chain 2 ventricular form, flk-1, α-fetoprotein and GATA-4.

Shamblott teaches embryoid bodies (EB's) produced from human primordial germ cells (hPGC's) (13729, col. 1, parag. 1-12). The EB's are taught by Shamblott to express markers of each embryonic germ layer: endoderm, mesoderm and ectoderm (page 13729, Table 1). In particular, Shamblott shows the EB's to express nonphosphorylated neurofilament heavy isoform, as indicated by reactivity with sm311, and to express α-fetoprotein, as indicated by reactivity with A008 (page 13728, col. 2, lines 2-4). An embryoid body is an enriched population of cells. Further, since the EB's taught by Shamblott and those disclosed in the present application are made by the same method, originating from hPGC's and have the same embryonic germ layers as indicated by marker expression, the EB cells of Shamblott would be expected by the ordinary artisan to undergo 30 or 60 population doublings. Further, the culture conditions taught by Shamblott for the culture of EB's clearly is non-permissive for human embryonic germ cells, and lacks LIF or a

fibroblast feeder layer (page 13727, col. 1, parag. 2, lines 1-4). The cells of Shamblott inherently can be infected by a retrovirus or a lentivirus. Thus, Shamblott clearly anticipates the claimed invention.

Claims 22, 27 and 30-32 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Shamblott et al (1998) Proced. Natl. Acad. Sci. 95, pp. 13726-13731.

Shamblott teaches a method of making an enriched population of cells comprising culturing hPGC's to form cystic EB's, dissociating the cystic EB's to provide a constituent cell and culturing the constituent cells in serum containing media, the constituent cells simultaneously expressing at least a first and second polypeptide or mRNA marker from at least two different cell types, wherein the cell types are selected from ectodermal cells, mesodermal cells, or endodermal cells, and wherein the first marker is selected from the group consisting of nestin, vimentin, neurofilament light isoform, microtubule-associated protein 2c, tau, nonphosphorylated heavy isoform, neuron-specific enolase, tyrosine hydroxylase, glial fibrillary acidic protein, CNPase, and galactocerebroside, and the second marker is selected from the group consisting of myf-6, myosin light-chain 2 ventricular form, flk-1, α-fetoprotein and GATA-4 (page 13729, col. 1, parag. 1, lines 1-4, parag. 2, lines 1-3; parag. 1, line 1 to col. 2, line 4 and page 13728, col. 2, lines 2-4). The EB's were dissociated from the original culture by plating them on tissue culture plates in the absence of LIF, FGF and forskolin (page 13727, col. 1, parag. 2, lines 1-4). The tissue culture plate provides a matrix. The EB's cells are cultured in a media not permissive for EG cell growth, which are growth in the presence of LIF, FGF and forskolin (page 12727, col. 1, lines 8-11). The EB cells would inherently be capable of 30 population doublings. Thus, Shamblott clearly anticipates the claimed invention.

Claims 1, 15 and 16 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Shamblott et al (1998) Proced. Natl. Acad. Sci. 95, pp. 13726-13731.

Claim 1 is drawn to an enriched population of cells comprising cells not having teratogenic properties in SCID mice, and express at least a first and second polypeptide or mRNA marker from at least two different cell types, wherein the cell types are selected from ectodermal cells, mesodermal cells, or endodermal cells, and wherein the first marker is selected from the group consisting of nestin, vimentin, neurofilament light isoform, microtubule-associated protein 2c, tau, nonphosphorylated heavy isoform, neuron-specific enolase, tyrosine hydroxylase, glial fibrillary acidic protein, CNPase, and galactocerebroside, and the second marker is selected from the group consisting of myf-6, myosin light-chain 2 ventricular form, flk-1, α-fetoprotein and GATA-4. Claims 14 and 15 are to the cells of claim 1, where the cells are clonally derived.

Shamblott teaches embryoid bodies (EB's) produced from human primordial germ cells (hPGC's) (13729, col. 1, parag. 1-12). The EB's are taught by Shamblott to express markers of each embryonic germ layer: endoderm, mesoderm and ectoderm (page 13729, Table 1). In particular, Shamblott shows the EB's to express nonphosphorylated neurofilament heavy isoform, as indicated by reactivity with sm311, and to express α-fetoprotein, as indicated by reactivity with A008 (page 13728, col. 2, lines 2-4). An embryoid body is an enriched population of cells. The clonally derived cells of claims 14 and 15 are taught by the specification to express markers of more than one embryonic germ layer. Thus, the EB's of Shamblott, composed of cells of each germ layer, are the same cells as those of claims 14 and 15. Alternatively, the cells of claims 14 and 15 are obvious over those of Shamblott because there is no distinction between them, as both Shamblott's cells and those claimed express the same marker. The term "clonal" is a method of producing the

claimed cells. If the method of producing a produce doesn't provide a novel and non-obvious property to a known product, the known product is not patentable.

The patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it, which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product (*In re Ludtke*). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). The human hematopoietic cells presently claimed cannot be distinguished over those of Bhatia. Furthermore, there is no evidence that applicant's disclosed method of producing the claimed cells imbues any new or novel/nonobvious features to the cells. Applicant, as stated above, should point out any such differences in response to this office action. The burden has been now shifted to applicant to argue or demonstrate a patentable difference.

Claims 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shamblott et al (1998) Proced. Natl. Acad. Sci. 95, pp. 13726-13731 view of Vittet et al. (1996) Blood 88, pp. 3424-3431.

Shamblott teaches a method of making an enriched population of cells comprising culturing hPGC's to form cystic EB's, dissociating the cystic EB's to provide a constituent cell and culturing the constituent cells in serum containing media, the constituent cells simultaneously expressing at least a first and second polypeptide or mRNA marker from at least two different cell types, wherein the cell types are selected from ectodermal cells, mesodermal cells, or endodermal cells, and wherein the first marker is selected from the group consisting of nestin, vimentin, neurofilament light isoform, microtubule-associated protein 2c, tau, nonphosphorylated heavy isoform, neuron-specific enolase, tyrosine hydroxylase, glial fibrillary acidic protein, CNPase, and galactocerebroside, and the second marker is selected from the group consisting of myf-6, myosin light-chain 2 ventricular form, flk-1, α-fetoprotein and GATA-4 (page 13729, col. 1, parag. 1, lines 1-4, parag. 2,

lines 1-3; parag. 1, line 1 to col. 2, line 4 and page 13728, col. 2, lines 2-4). The EB's were dissociated from the original culture by plating them on tissue culture plates in the absence of LIF, FGF and forskolin (page 13727, col. 1, parag. 2, lines 1-4). Vittet teaches the growth of cells isolated from mouse EB's in the presence of human basic fibroblast growth factor to initiate differentiation into vascular structures, and observed the expression of various endothelial cell markers (page 3427, col. 1, parag. 1, lines 2-8). Thus, at the time of present invention, it would have been obvious to the ordinary artisan to culture the EB cells of Shamblott in the presence of human bFGF (FGF2) to determine the effect of the growth factor on endothelial and vascular cell development on human EB cells.

Claims 22, 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shamblott et al (1998) Proced. Natl. Acad. Sci. 95, pp. 13726-13731.

Shamblott teaches a method of making an enriched population of cells comprising culturing hPGC's to form cystic EB's, dissociating the cystic EB's to provide a constituent cell and culturing the constituent cells in serum containing media, the constituent cells simultaneously expressing at least a first and second polypeptide or mRNA marker from at least two different cell types, wherein the cell types are selected from ectodermal cells, mesodermal cells, or endodermal cells, and wherein the first marker is selected from the group consisting of nestin, vimentin, neurofilament light isoform, microtubule-associated protein 2c, tau, nonphosphorylated heavy isoform, neuron-specific enolase, tyrosine hydroxylase, glial fibrillary acidic protein, CNPase, and galactocerebroside, and the second marker is selected from the group consisting of myf-6, myosin light-chain 2 ventricular form, flk-1, α-fetoprotein and GATA-4 (page 13729, col. 1, parag. 1, lines 1-4, parag. 2, lines 1-3; parag. 1, line 1 to col. 2, line 4 and page 13728, col. 2, lines 2-4). The EB's were dissociated from the original culture by plating them on tissue culture plates in the absence of LIF, FGF and forskolin (page 13727, col. 1, parag. 2, lines 1-4). At the time of the instant

invention, the formation of a clonal culture from a single cell would have been obvious to the ordinary artisan to create a cell population having the same biochemical characteristics. Further, RPMI 1640 was a well-known cell culture media, and the determination of the most effective growth conditions for a cell population was within the scope of skills of the ordinary artisan at the time of the instant invention. Likewise the determination of components of a culture media to optimize growth of a cell culture was well known and within the scope of skills of the ordinary artisan at the time of the instant invention.

Claims 22, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shamblott et al (1998) Proced. Natl. Acad. Sci. 95, pp. 13726-13731 in view of Rohwedel et al (1996) Cell Biol. Internat. 20, pp. 579-587.

Shamblott teaches a method of making an enriched population of cells comprising culturing hPGC's to form cystic EB's, dissociating the cystic EB's to provide a constituent cell and culturing the constituent cells in serum containing media, the constituent cells simultaneously expressing at least a first and second polypeptide or mRNA marker from at least two different cell types, wherein the cell types are selected from ectodermal cells, mesodermal cells, or endodermal cells, and wherein the first marker is selected from the group consisting of nestin, vimentin, neurofilament light isoform, microtubule-associated protein 2c, tau, nonphosphorylated heavy isoform, neuron-specific enolase, tyrosine hydroxylase, glial fibrillary acidic protein, CNPase, and galactocerebroside, and the second marker is selected from the group consisting of myf-6, myosin light-chain 2 ventricular form, flk-1, α-fetoprotein and GATA-4 (page 13729, col. 1, parag. 1, lines 1-4, parag. 2, lines 1-3; parag. 1, line 1 to col. 2, line 4 and page 13728, col. 2, lines 2-4). The EB's were dissociated from the original culture by plating them on tissue culture plates in the absence of LIF, FGF and forskolin (page 13727, col. 1, parag. 2, lines 1-4). Rohwedel teaches the culture of mouse EB cells on tissue culture plates coated with gelatin for morphological

studies (page 580, col. 2, parag. 1, lines 14-18). It is noted that gelatin is a hydrolyzation product of collagen I. Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to plate the EB cells of Shamblott on gelatin coated plates in order to study their morphology.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 7:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

January 7, 2006